

Atherosclerotic Vascular Disease in the Autoimmune Rheumatologic Patient

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Abstract Autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, have a strong association with an increased risk of atherosclerotic cardiovascular diseases (ASCVD), particularly ischemic heart disease (IHD). A majority of the autoimmune conditions occur predominantly in women, and as women continue to experience a higher cardiovascular mortality compared to men, this potential added risk factor must be recognized. Inflammation and immune mechanisms have been shown to be an underlying mechanism for the development of atherosclerosis, thus sharing a common mechanism with rheumatologic conditions. There is an under recognition, in both patient and physician, of the increased cardiovascular (CV) risk within the autoimmune population, with present CV risk profile algorithms performing poorly in these patients. Traditional risk factors play a role in the development of IHD in the autoimmune patient, but their overall significance is unclear and does not fully explain the elevated CV risk. The role of inflammation and risk factors in autoimmune conditions, and their link to the elevated CV risk will be explored within this article.

Keywords Inflammation · Autoimmunity · Atherosclerosis · Atherosclerotic vascular disease · Cardiovascular risk · Risk factors

Introduction

Systemic autoimmune rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SS), spondyloarthropathies, and vasculitides are inflammatory disorders which can all have cardiovascular (CV) manifestations. These manifestations may, in fact, be the initial presentation of the rheumatologic condition. Coronary atherosclerosis confers the most significant CV risk to the autoimmune patient, despite the fact that any cardiac structure may be affected. The majority of these autoimmune conditions affects women more often than men and therefore need to be included when discussing gender-specific issues with relationship to cardiovascular disease (CVD). Current algorithms for CV risk assessment in women include autoimmune disease in the “at risk” category [1]. However, autoimmune conditions presently are not included in any CV risk calculator. Rheumatoid arthritis and SLE have long been recognized as having excess atherosclerotic cardiovascular disease (ASCVD) risk [2, 3]. The other autoimmune inflammatory disorders have been less well studied given their lower prevalence, but early reports in antiphospholipid antibody syndrome (APS), SS, and psoriatic arthritis suggest similar increased CV risk [4–6]. As therapies for autoimmune diseases have improved over the last several decades, increasing patient longevity, the risk of premature atherosclerosis has become more clinically evident. It is now accepted that accelerated atherosclerosis is the leading cause of morbidity and mortality in the patient with a systemic autoimmune disease. Atherosclerosis itself has been identified as an inflammatory condition [7], and it is well established that systemic markers of inflammation independently predict ischemic heart disease [8]. Similarities exist between the inflammatory and immune-mediated mechanisms of both atherogenesis and autoimmune diseases, allowing the understanding of two diseases under one pathobiology.

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Inflammation and Immunity in Atherosclerosis and Autoimmune Diseases

Atherosclerosis is an insidious disease of the arteries that begins early in life and progresses. Hypercholesterolemia was recognized to play a major role in the development of atherosclerosis in the twentieth century. Mechanical and chemical stresses were felt to be initiators of the migration of smooth muscle cells into arterial lesions. When it was identified that lipid-laden foam cells were monocyte-derived macrophages, immunity was recognized as playing a major part [9]. The theory that cellular immunity played a major role was proposed when T lymphocytes and their subsequent activation were detected within human atherosclerotic plaques [10, 11]. Subsequently, other advances, including the discovery of autoantibodies, T cell subtypes, and humoral and cellular immunity in atheroprotection, have led to greater understanding of the relationship between atherosclerosis and autoimmune diseases. Atherosclerosis is a chronic disease where both innate and adaptive immuno-inflammatory mechanisms are involved. Inflammation is pivotal at all stages of the development of atherosclerosis. Autopsy studies indicate that in a patient with RA there might be more inflammation within the coronary atherosclerotic plaque, with a greater proportion of B cells, than what is seen in the non-RA patient, indicating that the mechanism of ischemic heart disease may be different between the two groups [12].

Early in the course of atherosclerosis, plaque formation is favored in vascular beds characterized by higher expression of proinflammatory mediators. This is the process of inflammatory signaling. These mediators include leukocyte adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), vascular endothelial growth factors, and cytokines [13]. Proinflammatory cytokines, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) expressed by the endothelium promote further leukocyte infiltration, proliferation, and activation. Immune dysregulation enhances this process.

Innate immunity is independent of antigenic stimulation and thus represents a nonspecific inflammatory response. Macrophage foam cells mediate this response in atherosclerosis and are the first immune cells at the arterial wall, serving as an on-site lipid reservoir. These foam cells become the source for the proinflammatory mediators. Superoxide anion is produced within the plaque via the macrophages phagocytic actions. All of these functions promote further inflammation and further progression of the plaque [14].

An antigen-specific, or adaptive, immunity has also been recognized in atherosclerosis [14, 15]. Adaptive immunity refers to T cells, immunoregulatory cytokines, and antibodies involved in plaque progression. Oxidized low-density lipoprotein (LDL), heat shock proteins, beta2 glycoprotein 1b, and infectious agents are autoantigens delivered by antigen-

presenting cells, within atherosclerotic lesions, to the T cells. Of these, oxidized LDL appears to be a primary antigen [16]. Detection of anti-oxidized LDL antibodies in atherosclerosis further supports the role of an immune reaction against the oxidized LDL that is present within the atherosclerotic plaque.

In rheumatoid arthritis, there is evidence that both immune dysregulation and systemic inflammation lead to the development of atherosclerosis, which may actually be identified before RA disease manifestations. Some evidence suggests that the excess CV risk precedes the diagnosis of RA [17]. Mortality from premature ASCVD is seen early in the course of seropositive RA [18], suggesting that preclinical inflammation is already exacting an influence on the coronary vasculature. The chronic inflammatory infiltrates seen in RA synovitis are similar to the cellular infiltrates seen within an atherosclerotic plaque. Mononuclear cell recruitment, proinflammatory cytokines, along with upregulation of adhesion molecules are present within inflamed RA-involved joints as well as within atherosclerotic lesions [19]. The erosions of cartilage and bone in RA are promoted by collagen-digesting enzymes, which also appear to play a role in atherosclerotic plaque rupture [4]. TNF-alpha, a cytokine prominent in RA, promotes a cascade of inflammatory mediators which include IL-1, IL-6, IL-8, prostaglandins, and matrix metalloproteinases which perpetuate and accelerate the inflammation seen in atherosclerosis [19]. This process of accelerated inflammation is fostered by an immune dysregulation seen in the autoimmune rheumatologic patient. Autoantibodies to oxidized LDL have been found in greater numbers in patients with autoimmune rheumatic diseases than in controls [20]. Confirming the link between atherosclerosis and RA is the presence of an abnormal CD4+ T cell in both processes [21]. Signaling Toll-like receptor (TLR), which is expressed by innate immune cells, plays a role in regulating antibody production in RA and SLE and is seen in atherosclerosis [22].

Similar to RA, commonalities exist between atherogenesis and SLE. Lupus may be considered a classic model of a systemic autoimmune disease. The pathogenesis of SLE includes the formation of immune complexes with complement activation. The autoantibodies, along with local inflammation as described above with RA, underlie the vascular injury and thrombosis seen in SLE [23]. Complex autoantibody production in SLE imparts the major role in the atherosclerosis production and progression [24].

Other rheumatologic conditions that are more common in women, such as SS and APS, have also been shown to exhibit accelerated atherosclerosis [4, 25]. Inflammation and autoimmunity underscore the pathogenesis of atherogenesis seen in these conditions, similarly to RA and SLE (but possibly in varying degrees). In APS, the presence of circulating antiphospholipid antibodies (aPL) appears to be the mediator of proinflammatory and prothrombotic effects on the vasculature [26]. Some of these antibodies seem to be able to cross react with oxidized LDL in SLE [27].

Epidemiology of Atherosclerotic Cardiovascular Disease in Autoimmune Rheumatologic Diseases

Understanding the similarities between atherosclerosis and autoimmune diseases establishes the basis for the recognition of the increased CV morbidity and mortality seen in this patient population [3–6]. SLE and RA have the largest body of available literature describing the increased burden of ASCVD, but smaller studies suggest an increased burden of ASCVD risk in APS and SS. Sjogren's, another female predominant autoimmune rheumatologic disease, has several clinical manifestations similar to SLE, including circulating autoantibodies, and also shares some features with RA, such as rheumatoid factor (RF) and joint inflammation, however has not consistently been shown to have a higher prevalence of ASCVD.

SLE is a disease that affects 5 to 6 people per 100,000. It is nine times more common in women than men. The disease can have an onset at any point in life, but typically is seen most commonly between the ages of 16 to 55. Patients with lupus have a considerably increased morbidity and mortality related to ASCVD [28]. In SLE, there is a bimodal pattern of mortality, with an early peak (within the first three of years of diagnosis) related to active disease, sepsis, and nephritis, and a later peak (greater than 5 years from diagnosis) due to myocardial infarctions [3]. Patients with SLE have a fivefold to sixfold increased risk of CV events compared to the general population [29] and have been identified as having more atherosclerotic plaque within coronary arteries, as assessed by coronary calcium computed tomography [30]. Young women with SLE were more than two times more to experience myocardial infarctions (MI) compared with young women without lupus in a retrospective study from California. In this study, women older than 45 experienced no difference in the rate of hospitalization for acute MI whether they had SLE or not [28]. In the Pittsburgh SLE cohort, 67 % of women with lupus were less than 55 years of age at the time of their first cardiac event [29]. This translated to women between the ages of 35–44 having a relative risk of MI over 50 times that observed in age-matched controls. The relative risk in older women was also increased but only two- to fivefold higher. In patients who undergo coronary revascularization, there does not appear to be any significant difference between SLE and non-SLE patients in the prevalence of multivessel disease or in the reasons for revascularization (asymptomatic coronary artery disease (CAD), stable angina, unstable angina, and MI). The need for urgent and emergent procedures was also similar between groups. However, the patient with SLE who did undergo percutaneous coronary interventions (PCI) had more adverse events following these procedures, such as repeat PCI and myocardial infarction MI's, compared with non-SLE patients after adjustments for covariates [31, 32]. A 2004 study out of California did not find a difference in in-hospital mortality

after an acute MI between patients with SLE and those without, after adjusting for co-variables [33]. Methodology may account for some of these differences.

Antiphospholipid antibody syndrome occurs either as a primary condition or in the setting of an underlying disease, usually SLE. The incidence of the APS is around 5 new cases per 100,000 persons per year. The syndrome is defined by the presence of one type of autoantibody (aPL) and the occurrence of either venous or arterial thromboses or pregnancy morbidity (or a combination). APS is characterized by a prothrombotic states where recurrent venous and arterial thromboembolisms occur. The development of atherosclerosis appears to be linked to the presence of the circulating aPL and may be the first manifestation of APS [34, 35]. A substudy of the Helsinki Heart Study evaluated the relationship of aPL (specifically anti-cardiolipin antibodies (aCL)) to myocardial infarctions. Although only men were studied, those with the highest aCL levels had a relative risk for myocardial infarction of 2.0, compared with the remainder of the population and independent of confounding factors, such as age, smoking, systolic blood pressure, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) [36]. However, given variabilities in study results, the role of aPL and/or APS as independent risk factors for atherosclerosis remains somewhat unclear [37]. The pro-coagulant activity of antiphospholipid antibodies may be the driver for ischemic events rather than atherosclerotic plaque formation [38].

Systemic sclerosis is a disease that affects the microcirculation, which is manifested as Raynaud's phenomenon, pulmonary arterial hypertension, and scleroderma renal crisis. Endothelial dysfunction and inflammation may lead to macrovascular dysfunction and ultimately atherosclerosis. In a population-based cohort of patients with SS, the risk of incident MI was increased approximately twofold compared to matched controls [39]. In a recent Chinese study, SS was associated with an increased risk of acute myocardial infarction; however, less than 40 % had obstructive coronary artery disease, indicating that microvascular abnormalities may be the primary mechanism rather than epicardial coronary artery stenosis [5].

Rheumatoid arthritis has the most abundant epidemiological data given its greater prevalence. RA prevalence is estimated at approximately 1 % in Caucasians. The annual incidence is around 40 per 100,000 and affects women two to three times more often than men. The mean age at onset is around 56 years old. Over a period between 1955 and 1994, higher rates of death were noted in the RA patient, with women having more excessive mortality compared to men [40]. The increased morbidity and mortality in RA has been found to be due to ASCVD. In fact, woman with RA have higher risk of an acute MI than men with RA [41]. A meta-analysis, encompassing 24 observational studies of RA mortality between 1970 and 2005, found that CV mortality was significantly increased (overall standard mortality ratio of 1.50 with 95 % confidence interval (CI)). The standard mortality ratio

for ischemic heart disease (IHD) was similarly increased at 1.59 (95 % CI). In a prospective cohort study involving over 110,000 women who participated in the Nurse's Health Study, women with RA had a twofold higher risk of myocardial infarction [42]. Post-MI 30-day CV mortality has been shown to be higher in RA compared to non-RA patients (odds ratio (OR) for CV death in RA patients following a first acute CV event, which included MI and stroke, was 1.6 (95 % CI 1.2–2.2)). The increased mortality was accounted for almost entirely by excess deaths following MIs [43]. Despite the increased risk of IHD, patients with RA are less likely to experience angina and more likely to have no symptoms before sudden cardiac death. The risk of sudden death in RA is two times more likely than in a non-RA patient and an unrecognized MI is also twice as common [44]. An increased CAD risk may actually predate the diagnosis of RA; patients diagnosed with RA have a three times higher likelihood of a prior MI compared with non-RA individuals [44]. This suggests that premature or accelerated atherosclerosis may occur before or with RA symptom onset, but likely still before RA diagnosis. Others have not identified an increased risk of IHD before RA symptom onset [45]. There have been some reports of a decline in ASCVD mortality in the RA patient (specifically in acute MI mortality) [46]; however, this decline has not been as dramatic as what has been observed in the general population, thus the mortality gap appears to be widening [47]. There have been varying reports on the approaches to treatment of MIs between the RA patient and the non-RA patient. There have been reports suggesting a lower likelihood of an RA patient to receive acute reperfusion after an acute MI, along with lower rates of utilization of proven post-MI medications [48]. Others have found in patients presenting with MIs, those with RA may in fact receive more acute reperfusion and have an in-hospital survival advantage [49, 50]. Long-term mortality has been shown however to be poorer in the RA patient post-MI, despite similar MI treatments, indicating possibly the influence of the RA disease characteristics as the determinant for long-term survival after an MI [51].

Traditional Cardiovascular Risk Factors in Autoimmune Diseases

Traditional risk factors for coronary artery disease include advancing age, the present of hypertension (HTN), hyperlipidemia, diabetes mellitus (DM), and male gender. These traditional risk factors have been used in CV risk scoring calculators such as the Framingham score and the Systemic Coronary Risk Evaluation (SCORE) which are most often used in Europe. In addition to these classic risk factors, the metabolic syndrome, which requires three or more of the following: abdominal obesity, increased fasting blood sugar (≥ 100 mg/dL), elevated triglycerides (TG) (≥ 150 mg/dL) or treatment of

an elevated TG, blood pressure $\geq 130/85$ mmHg or drug treatment for elevated blood pressure, and low serum HDL (<40 mg/dL in men and <50 mg/dL in women), incurs an increased risk of cardiovascular disease as well as an increased risk of developing type II DM [52]. Thus, the question regarding the increased ASCVD seen in the rheumatologic patient is whether these traditional risk factors are more prevalent than that seen in the general population or whether their occurrence is similar to the general population but act differently. Again, the literature regarding these questions is primarily in the RA patient and secondarily in the SLE patient. The focus thus will be how these traditional risk factors play a role in these two groups.

Tobacco use is a very important risk factor for IHD as well as being a risk factor for the development of RA, particularly seropositive RA (those with positive rheumatoid factor and more importantly positive anticitrullated protein antibody (ACPA)) [53, 54]. In the Nurses' Health Study, past cigarette smoking was more likely in the women with RA than in those without RA (48 versus 38 %) [42]. A meta-analysis reported in 2011, which included 15 studies, also found the prevalence of smoking to be higher in the RA patient with an odds ratio of 1.56 (85 % CI; 1.35–1.80) with a p value of <0.00001 [55]. Thus, smoking risk may explain part of the increased CV risk in the RA patient. In fact, carotid intimal medial thickness (CIMT), a marker of early atherosclerosis, has been shown to be greater in current RA smokers compared to nonsmoking RA patients [56]. However, the importance of this risk factor may be less in the RA patient compared with the smoking risk in a non-RA patient. A retrospective study which reviewed whether traditional CV risk factors conferred the same risk among RA and non-RA patients found that smoking had less of a risk in the RA patient compared to control (the hazard ratio was 1.3 in the RA smoker compared to 2.2 in the non-RA smoker; 95 % CI) [57]. So, although smoking is not only a risk factor for the development of RA and does impart a risk for IHD in RA, its overall effect may be less significant than in the patient without RA. In SLE, there have been some conflicting reports on the prevalence of smoking, with the Toronto cohort showing similar smoking rates between SLE patients and the general population (relative risk 0.86, 95 % CI) [58], but the Systemic Lupus International Collaborative Clinics (SLICC) registry revealed increasing trends of smoking in the SLE population over a 3-year period [59]. Smoking in SLE has been related to vascular events in both the Toronto group [60] and the SLICC registry [61], but in the Johns Hopkins Lupus Cohort, smoking was not related to CAD [62], nor was it related to the presence of carotid plaque in the Pittsburgh Lupus cohort [63].

Cholesterol abnormalities have become a vital component in our CV risk algorithms such as Framingham. In the general population, using the cholesterol profile has become a routine part of the CV risk assessment. In RA, hyperlipidemia (elevated

TC or LDL cholesterol) appears to occur less commonly than in the general population [64, 65•] but, despite this, results in higher rates of acute myocardial infarctions and ischemic stroke [66]. Women with RA have significantly lower TC and LDL cholesterol compared to the general population but interestingly with no significant differences in HDL based on a study of 2005 RA patients [65•]. The decrease in TC and LDL cholesterol actually appears to occur 3–5 years prior to the onset of the diagnosis of RA [67]. High-grade inflammation (either during acute episodes or with chronic high levels of inflammation) suppresses TC and LDL levels but results in an even greater suppression of HDL cholesterol, which produces the deleterious atherogenic index (TC/HDL cholesterol ratio) [68]. This seems to explain why the elevated TC and LDL occur less commonly in the RA patient. A meta-analysis suggested that in RA, the most common lipid abnormality was actually a depressed HDL cholesterol [55]. In fact, a paradoxical relationship now appears to exist between lipid abnormalities and ASCVD risk in the RA patient, whereby lower TC and LDL levels are associated with increased cardiovascular risk [69]. In this population-based incidence cohort of RA patients, the level of inflammation (particularly erythrocyte sedimentation rates (ESR)) correlated most closely with ASCVD risk. As ESR increased, lower TC/HDL ratios were associated with higher CV risk; thus, the association of lipids to ASCVD risk is affected by the level of inflammation present [69]. In SLE, elevated TC and LDL cholesterol do not seem to occur with any greater frequency compared to the general population, although higher TG and very low-density lipoproteins (VLDL) have been observed [58]. However, if there is a combination of SLE and hypercholesterolemia, an 18-fold increased risk of MI is observed compared to the general population [41].

Hypertension is very common worldwide and imparts a significant but modifiable risk for the occurrence of myocardial infarctions [70]. As in the general population, HTN is common in patients with both RA and SLE. In RA, a recent meta-analysis showed that HTN has a similar prevalence compared to the general population (OR 1.09, 95 % CI) [55]. An older study with substantially larger number of patients suggested a higher prevalence of HTN in RA (relative risk 1.3) [71]; this study showed a similarly increased relative risk of HTN in the patient with psoriatic arthritis and ankylosing spondylitis [71]. A Greek study suggested that the presence of HTN incurred a significant risk for ASCVD (hazard ratio 3.76, 95 % CI 0.99–15.06). HTN however is complex in that it can be influenced by many other factors, such as inactivity, obesity, and certain medication; thus, its overall role in RA is more difficult to characterize independently. However, there are reports that HTN may be underdiagnosed in the RA patient, as well as being undertreated [72]. In SLE, HTN is significantly more common than the general population with a relative risk of 2.59 (95 % CI) [58]. Also, HTN has been linked to vascular events and mortality in SLE [61, 73].

Diabetes as well and insulin resistance occur with a higher prevalence in RA patients compared to controls [55, 74]. Insulin resistance is linked to inflammatory markers, such as TNF α , IL-6, ESR, and CRP, as well as disease activity in RA [75, 76]. Metabolic syndrome similarly is seen more commonly in RA [77, 78]. Abdominal obesity affects the glucose metabolism in RA [74] as it does in the general population. Likewise in SLE, the prevalence of diabetes is significantly increased [58], but interestingly has not been shown to confer an increased risk of CV events compared to the general population. Insulin resistance, which also is more frequent in SLE compared to the general population, is related to ESR [76], but also does not appear to predict ASCVD risk. Whether the increased prevalence of diabetes and metabolic syndrome is independently related to the autoimmune condition is unclear. These patients' use of glucocorticoids along with abdominal obesity, sedentary lifestyle, and the underlying autoimmunity/inflammation all contribute adversely to glucose metabolism.

Obesity is known to decrease life expectancy [79] and has been identified by the American Heart Association as an independent risk factor for ASCVD. Obesity has been associated with the development of RA [80] with those in the highest quartile of body mass index (BMI) having the highest risk relative to the lowest quartile (relative risk 1.4 (95 % CI= 1.0–2.0)) [81]. As in the general population, the presence of obesity in RA patients is associated with the presence of traditional risk factors [82]. However, there is an interesting association with BMI and mortality in RA. RA patients with a lower BMI have a significantly increased risk of CV death even after adjusted for co-variables [83]. This paradox may be related to uncontrolled systemic inflammation, with the highest ESR levels mitigating the protective effects of a high BMI [84]. In SLE, obesity has been shown to be a risk factor for atherosclerotic events [61]. An elevated BMI in SLE is also a major factor for the development of insulin resistance in patients with SLE [76].

So, we see that traditional risk factors are clearly important in the CVD risk assessment in the patient with rheumatologic diseases. However, not all factors have the same impact on overall CV risk in the autoimmune patient compared to the general population. In addition, these risk factors alone do not fully account for the accelerated CV risk observed in these patients [85••, 86]. Using the Framingham and Reynolds risk scores in patients with RA underestimates the CVD risk significantly, more so for the older patient and those who are seropositive [85••, 87]. The absolute ASCVD risk in RA is similar to the risk in a non-RA patient who is 5–10 years older [88]. The RA patient has a similar CV morbidity and mortality as the patient with diabetes [89], yet is not recognized as such with present risk algorithms. In patient with SLE and ASCVD, one fewer traditional risk factor is present compared to the general population with ASCVD [60, 90]. After adjusting for the Framingham score in the SLE patient, there

remains a 7.5–17-fold increased risk of CV events [86]. So, there must be other factors to consider when determining the overall ASCVD risk in an autoimmune patient.

Nontraditional Cardiovascular Risk Factors in Autoimmune Diseases

As noted previously, the role of inflammation is vital to the understanding of atherosclerosis. The autoimmune patient thus has the increased burden of inflammation that imparts an added risk of ASCVD. Markers of inflammation such as fibrinogen and CRP levels have been found to be higher in woman with RA compared with controls in the Nurses' Health Study [91]. Other potential factors that may play a role are the cytokines interleukin-17 [92] and TNF-alpha [93]. The markers of disease activity in RA, such as CRP and ESR, have been linked to CVD risk [44, 94]. Also, the disease severity, measured by rheumatoid factor (RF), ACPA, destructive joints with physical limitations, rheumatoid lung disease, and presence of rheumatoid nodules along with the use of corticosteroids, has been associated with CVD morbidity and mortality [95–98]. In SLE, along with inflammatory markers, evidence of organ involvement as well as disease-related damage scores has been associated with ASCVD [60, 99]. Going beyond the traditional cholesterol profile, a proinflammatory HDL, which does not confer protection for LDL cholesterol oxidation, has been seen in higher levels in patients with SLE and RA [100].

A number of medications used in autoimmune rheumatologic diseases may also play a role in the risk profile. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with ASCVD and their use must be tempered with the overall CV risk in an individual patient [101]. Corticosteroids, as well as NSAIDs, are associated with development of HTN. Steroids in addition can cause weight gain, insulin resistance, and adverse lipid profiles which can contribute to the increased ASVD risk. Use of steroid monotherapy has been linked to a 50 % increased risk of a CV event [102]. Use of methotrexate (MTX) and other disease-modifying drugs (DMARDs) in RA have been associated with decreased CV risk [103–105]. In fact, the use of MTX is being studied in the Cardiovascular Inflammation Reduction Trial (CIRT), funded by the National Heart, Lung, and Blood Institute (NHLBI) to assess whether MTX reduces vascular events in a high-risk population. Hydroxychloroquine, used in SLE, is associated with improved survival and a decrease in vascular events [106]. Anti-TNF agents have also been associated with improved CV outcomes [103]. The proposed mechanism for these potential benefits is related to the decrease in systemic inflammation. However, the true role of these agents in decreased CV risk remains unclear. These agents are prescribed based on levels of disease activity and severity as well as

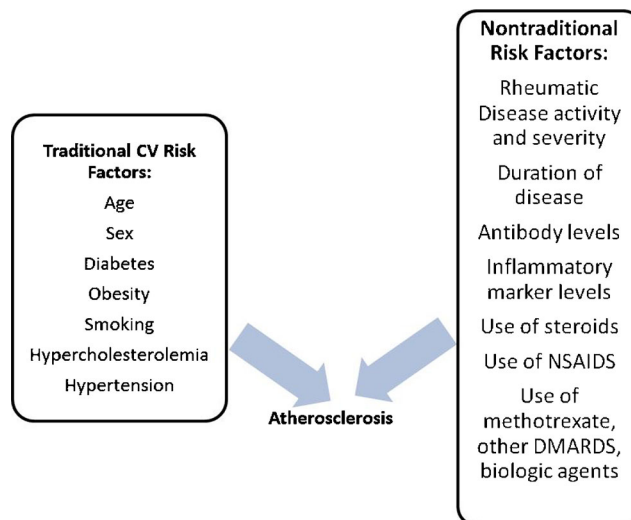


Fig. 1 Major variables contributing to atherosclerosis in autoimmune rheumatologic diseases (CV, cardiovascular; NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs)

based on individual patient profiles, and are frequently used in combination; thus, their effects on ASVD is confounded by various factors.

Conclusion

The autoimmune rheumatologic patient has an increased risk of ASCVD. There is a complex interplay between traditional and nontraditional risk factors in these patients (see Fig. 1). Inflammation appears to be the backbone on which the CV risk accelerates beyond the traditional risk factors. Present methods to evaluate CV risk in this patient population are underrepresenting the true risk. A collaborate approach to this high-risk patient population is essential. The traditional risk factors must be fully identified and treated aggressively. However, autoimmune disease severity and activity must be addressed with appropriate agents to modify the systemic inflammation. Whether initial evaluation of the autoimmune patient should include testing for early atherosclerosis, with surrogate markers such as CIMT, endothelial function assessment, and coronary artery calcium determination, is unclear, but warrants further study. The goal is to educate both the patient and provider regarding the elevated risk and incorporate multiple approaches to decrease that risk.

Compliance with Ethics Guidelines

Conflict of Interest Rekha Mankad declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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